of residues 32-237 or 32-234 or 34-233 of the native hGHR molecule, capable of being crystallized without being complexed to a ligand molecule, but does not reasonably provide enablement for a cytokine receptor protein of the Class I Cytokine family modified in the extracellular domain capable of being crystallized without being complexed to a ligand molecule.

As will be set forth in detail below, Applicants submit that the proteins defined by present claims 1, 2, 5-10 and 42-43 are fully enabled by the instant specification. Applicants wish to correct the apparently inadvertent mischaracterizations of the invention by the Examiner, and to dissuade the Examiner from applying an improperly exacting, nonstatutory enabling standard to the specification of this invention. Accordingly, these rejections are traversed and reconsideration is respectfully requested.

Instant independent claim 1 is directed to a cytokine receptor protein of the Class I Cytokine family, modified in the extracellular domain, wherein at least terminal molecule segment which contributes to a disordered structure is deleted, the modified protein being capable of being crystallized without being complexed to a ligand molecule. Independent claim 42 is directed more specifically to human growth hormone receptor protein comprising human growth hormone receptor protein truncated in at least one terminal end to delete at least one molecule segment which contributes to a disordered structure, the modified human growth hormone receptor protein being capable of being crystallized without being complexed to a ligand molecule.

The Examiner asserts the "nature of the invention is that $hGHR_{32-237}$, modified in the extracellular domain as instantly taught, can be crystallized without being complexed to a ligand molecule." The Examiner goes on to define (see OA, page 3) the novelty therein, stating that similarly modified cytokine receptor proteins, including those of the Class I Cytokine family, have not been recognized in the art as being capable of crystallization in the

absence of a ligand. Applicants find it puzzling that the Examiner perceives and states the novelty clearly, yet fails to confer the corresponding patentable breadth to the claims. Inherent in this statement of novelty, and throughout prosecution, the Examiner appears to accept that modification of this family of proteins, as taught in the specification to include deletion of at least one disordered region of at least one terminus of the extracellular domain, is within the capability of an ordinary person skilled in the art. In other words, it is enabled.

The Examiner repeatedly asserts that the art of crystallization of proteins is somewhat unpredictable, and that for unpredictable arts, a higher degree of guidance must be provided in order to practice the invention. However, the modified hGHR instantly claimed by Applicants is NOT crystallized. It is modified in a manner discovered by Applicants to render it *capable* of crystallization. That is, in fact, the essence of the invention. If an ordinary practitioner of the arts modifies a protein of the Class I Cytokine family such that it cannot be crystallized as taught by the specification, then that modified receptor is simply not within the scope of the invention.

Applicants fail to see where the level of experimentation involved in practicing the instantly claimed invention is undue. The means for modifying proteins into the instantly claimed proteins are well known in the art. First, as evidenced by references both cited in the specification and submitted with the last response to show the state of the art, identifying a Class I Cytokine receptor protein is routine, and was so at the time the instant application was filed. The Examiner cannot reasonably dispute this contention. Second, identifying the termini of an extracellular region of this receptor is routine. Third, as evidenced by references submitted with the last response to demonstrate state of the art, identifying disordered regions of those termini is within the capability of ordinary practitioners of the art, as disordered regions confined to termini are easily distinguishable from the ordered regions which comprise the tertiary structure of the protein.

The references demonstrate that such regions are observable upon super-visual inspection via means well-known in the art. The precise points of demarcation in terms of which amino acids to delete are empirically determinable. While it is true that practicing the invention involves truncating the termini at the point just before tertiary folding is implicated, which may involve some degree of hit and miss, what constitutes a "hit" and what constitutes a "miss" is obvious in light of the instant teachings. Creativity or any inventive step on the part of the skilled practitioner beyond the teachings of the instant specification is not required. The ordinary practioner need only follow the steps and observe an one of two outcomes. Yes, determining the disordered region that needs to be truncated requires some experimentation, coupled with X-ray or other visualization technology...but, the direction of the experimentation is fully guided by the specification and sources referenced for that purpose therein. The Examiner appears to be rejecting *any* experimental necessity, objecting in the OA at page 4, paragraph 1, that the region needing to be deleted to obtain the inventive protein must be experimentally identified.

The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, *or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed* to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 37 USPQ2d 1618, 1632 (Fed.Cir. 1996) (emphasis added).

Perhaps underpinning the Examiner's mischaracterization, she misconstrues the breadth of Applicants invention, asserting that the "Applicant...extrapolates this result into a conclusion that deletion of a *any terminal molecule segment* of any cytokine receptor protein of the Class I Cytokine family would lead to a protein that also can be crystallized without being bound to a ligand" (see OA page 4, paragraph 2, emphasis added). This is manifestly not what Applicants claim as their invention, and is, in fact, broader than the broadest instant embodiment - independent claim 1. Applicants are in complete agreement that if the instant specification provided no more guidance than "delete any terminal molecule segment", undue experimentation would be required to make the determination as to what to delete. On the contrary, Applicants invention involves the recognition, for the first time, that *deletion of a disordered region of the termini* of such a receptor results in a molecule which is capable of being crystallized without being complexed to a ligand molecule. Applicants claim is to the inventively modified, uncrystallized receptor, which is capable of such crystallization. The technician wishing to practice the invention is not left to guess randomly at what terminal segments to delete, but is sufficiently provided with guidance in the specification, specifically with respect to disordered regions, and more specifically with respect to disordered regions of the extracellular termini of this family of proteins.

In addition, Applicants submit that the Examiner is holding the present claims to a nonstatutory, unprecedented, over-exacting enablement standard. The Examiner asserts that the structural homology of cytokine receptors does not provide a basis for concluding that truncation of an extracellular domain of any cytokine receptor would enable its crystallization without being complexed to a ligand. Ignoring for a moment the perpetuated mischaracterization of the taught modification, Applicants further take issue with the underlying assertion. The Federal Circuit never held that enablement of claims directed to proteins required a precise, amino acid by amino acid description of that protein, or that

homology could not be used as the basis to draw reasonable inferences about behavior or function. The relevant Federal Circuit precedent only holds that disclosure of one or two species *may* not enable a broad genus, *e.g.*, *In re Vaeck*, 947 F.2d at 495-96, 20 USPQ2d at 1444-45, *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385 (Fed. Cir. 2003). But then again, it may. In *Amgen*, the Federal Circuit commented on the apparent merger of the *Lily* rule (*see Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1567-68 43 USPQ2d 1395, 1405 (Fed. Cir. 1997), which instituted exacting §112 written description standards for the specifications of genetic material claims, and the enablement requirement, and cautioned against morphing *Lily* into a nonstatutory, impermissable "superenablement" standard in biotechnology, stating that "in *Enzo* we clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. *Amgen Inc.*, 314 F.3d at 1332, 65 USPQ2d at 1396. Specifically, in *Enzo*, the Court rejected reliance on *Lily* with respect to enablement and found compliance for a broad genus claim where a correlation between function and a structure was disclosed. *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed.Cir. 2002). As the Enzo court noted, broad entitlement questions are policy matters that are not properly addressed by resorting to impermissible standards.

Further, Applicants fail to see the relevance of the Examiner's reference to lack of specific starting materials, or conditions under which a process is to be carried out. The Examiner correctly quotes case law in stating "it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." The Examiner already articulated that the novel aspect of the inventive proteins is the heretofore unrecognized discovery that modifying this class of

proteins as taught in the specification renders them capable of crystallization without being complexed to a ligand. The technical laboratory steps needed to practice this invention, i.e., identifying Class I cytokines, locating extracellular domain termini, determining disordered regions, and deletion of amino acids, are all well-known in the art. The Examiner appears to be confusing "labor intensive" with "undue". The specification does, indeed, enable the novel aspects, i.e., how to modify a protein to form the inventive protein, and recognition of the impact of this modification. Any challenge which one of ordinary skill might encounter in attempting to make and use the claimed invention using other Class I family cytokines can be resolved by experimentation falling far short of undue. To counter-phrase the succinct summary of the Examiner, the instant specification is enabling because one can follow the guidance presented therein and practice the claimed invention without any creative contribution.

It is believed the above represents a complete response to the 35 U.S.C. §112 ¶ 1 rejection of claims 1, 2, 5-8 and 42-43, set forth in the Official Action, and places the present application in condition for allowance. Reconsideration and an early allowance are respectfully requested.

Respectfully submitted,

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